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ORIGINAL ARTICLE

Carotid intima-media thickness in kidney transplant recipients

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KEYWORDS
ADMA;
cardiovascular risk;
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hs-CRP;
kidney transplantation

Abstract *Background/Purpose:* Cardiovascular disease is the leading cause of mortality among kidney transplant recipients. Carotid intima-media thickness (CIMT) of the common carotid artery is a surrogate marker for early atherosclerosis. We wanted to compare the prevalence of increased CIMT among kidney transplant recipients with matched controls and its association with clinical and laboratory parameters.

Methods: A comparative cross-sectional study involving kidney transplant recipients and controls matched for age, sex, chronic kidney disease staging, and cardiovascular risks was used. CIMT measurements were done using carotid ultrasound and considered increased if $>75^{th}$ percentile matched for age- and sex-matched normal controls. Standard laboratory investigations, high sensitivity C-reactive protein, and asymmetric diamethylarginine were analyzed.

Results: Thirty-six kidney transplant recipients (25 men, 11 women) with a median age of 41 years [interquartile range (IQR), 38–52 years] and 36 matched controls with a median age of 44 years (IQR, 37–53 years) were enrolled. There were no demographic differences between the two groups. Kidney transplant recipients had a significantly increased CIMT, 0.8 mm (IQR, 0.6–0.9) compared to matched-controls 0.55 mm (IQR, 0.5–0.7, $p = 0.001$). Two thirds of kidney transplant recipients had increased CIMT, which was associated with a higher low density lipoprotein (LDL) ($p = 0.022$) and higher hemoglobin ($p = 0.006$). Smoking status ($p = 0.058$) and male sex ($p = 0.073$) had a trend towards significance to increased CIMT. Multiple linear stepwise regression demonstrated both age and hemoglobin were independent predictors of CIMT ($p < 0.001$). We found no relationship between high sensitivity C-reactive protein and asymmetric diamethylarginine with CIMT.

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Conclusion: CIMT among our kidney transplant recipients was significantly higher compared to controls thereby increasing their cardiovascular risk.
背景: 心血管疾病是腎臟移植接受者的主要死因,總頸動脈的內膜中膜厚度 (CIMT) 則是早期動脈粥樣硬化的替代性指標。在本研究中,我們比較了 CIMT 增厚於腎臟移植接受者與匹配對照組之間的盛行率,並調查了 CIMT 與臨床及實驗室參數之間的關聯。
方法: 這是一項橫斷式比較性研究,涉及的對象包括腎臟移植接受者、及與其匹配 (年齡、性別、慢性腎病分期及心血管風險) 的對照者。CIMT 以頸動脈超音波測量,增厚的定義為對應年齡性別匹配正常對照組之 $> 75^{th}$ 百分位數。其他測量項目除了標準實驗室參數外,亦包括高敏感度 C-reactive protein (hs-CRP) 及 asymmetric diamethylarginine (ADMA)。
結果: 分析對象包括 36 位年齡中位數 41 歲 (38,52) 之腎臟移植接受者 (25 男、11 女) 及 36 位年齡中位數 44 歲 (37,53) 之匹配對照者,兩組間的人口學特徵並無不同。腎臟移植接受者之 CIMT 為 0.8 mm (0.6,0.9 mm),明顯高於匹配對照者之 0.55 mm (0.5,0.7 mm) ($p = 0.001$)。腎臟移植接受者之間,3 分之 2 呈現 CIMT 增厚的情形,較厚的 CIMT 與較高的低密度脂蛋白 ($p = 0.022$) 及較高的血色素 ($p = 0.006$) 有關。吸煙狀況 ($p = 0.058$) 及男性性別 ($p = 0.073$) 亦有傾向與 CIMT 增厚有關。多變項線性逐步迴歸分析顯示,年齡及血色素均是CIMT的獨立預測因子 ($p < 0.001$)。對於 CIMT 與 hs-CRP 或 ADMA 數值之間,我們並未發現明顯的關係。
結論: 在本研究的腎臟移植接受者中,CIMT 明顯高於對照組,因此具較高的心血管風險。

Introduction

Kidney transplantation not only improves quality of life in end-stage renal disease patients but also gives them a long-term survival advantage by reducing their mortality risk compared to maintenance dialysis.[1] Cardiovascular disease (CVD) is a major cause of morbidity and mortality in kidney transplant (KTx) recipients and death from CVD is the commonest cause of graft loss.[2] Although KTx recipients have a lower risk of fatal and nonfatal cardiovascular events compared to dialysis patients, their risk is much higher than the general population.[3] In addition to the traditional risk factors, nontraditional risk factors that contribute to CVD in KTx recipients include reduced kidney function post-transplantation, longer dialysis duration prior to transplantation, episodes of graft rejection, the effect of immunosuppressive drugs, hyperhomocysteinemia, and elevated levels of lipoprotein(a), C-reactive protein (CRP), interleukin-6, and asymmetric dimethylarginine (ADMA).[4–7] Accurate risk stratification of these patients will allow targeted interventions to prevent or limit adverse outcomes.

Atherosclerotic structural changes as detected by high-resolution B-mode ultrasound precede clinical findings by several decades. Endothelial dysfunction has been shown to be predictive of future cardiovascular events.[8] Although kidney function improves, endothelial dysfunction persists after transplantation and the true mechanism is still poorly understood.[9] Carotid intima-media thickness (CIMT) of the common carotid artery is a surrogate marker used to predict early atherosclerosis.[9,10] The prevalence of subclinical atherosclerosis measured by CIMT is greater in KTx recipients compared to the general healthy population.[3] Endothelial dysfunction and ongoing chronic inflammation due to multiple risk factors including immunosuppressive therapy play an important role towards premature subclinical atherosclerosis in KTx recipients.[11]

Previous studies have compared KTx recipients with healthy controls. Therefore, in our study we selected a control group who are not only matched for age but also CVD risk factors such as hypertension, diabetes mellitus, and staging of chronic kidney disease. We wanted to compare CIMT between KTx recipients and non-KTx matched controls and determine the factors influencing the CIMT in KTx recipients.

Methods

This was a comparative cross sectional study involving KTx recipients at Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, Malaysia, from January 2014 to August 2014. The study was approved by the UKMMC Ethics and Research Committee (Study Code FF-2014-022). All KTx recipients attending the nephrology outpatient clinic at our institution were screened. KTx recipients $>$ 6 months post-transplantation, aged $\geq$ 18 years and on stable triple immunosuppressive therapy for $>$ 6 months were included. We excluded patients with documented CVD (ischemic heart disease, stroke, peripheral artery disease) and any patients who were pregnant. The matched control group was selected from volunteers matched for age, sex, chronic kidney disease staging, underlying hypertension, and diabetes mellitus from nephrology and medical clinics in UKMMC. We excluded controls who were either pregnant, had documented CVD, or were on any immunosuppressive therapy.

After obtaining informed consent, history regarding previous cardiovascular events (defined as any coronary event such as myocardial infarction, angioplasty or coronary artery bypass surgery, and cerebrovascular accident) were obtained from patients' medical records. Baseline blood investigations for hemoglobin level, renal profile, fasting blood sugar, glycated hemoglobin, and fasting lipid profile were collected from both groups of patients. High-sensitivity CRP (hs-CRP) and ADMA were collected only in KTx recipients.

In addition to a mean of two seated blood pressure (BP) readings, ambulatory BP monitoring was carried out in KTx recipients using the BPRO machine (model T6400; Healthstats, London, UK). BP readings were taken at 15-minute

intervals throughout the daytime and 30-minute intervals during the night. Mean 24-hour daytime, night-time systolic and diastolic BP, and mean arterial BP were derived from 24-hour ambulatory BP monitoring. For the control group, a mean of two seated blood pressure readings was recorded to ascertain their status of hypertension. Hypertension was defined as systolic arterial pressure $>$ 140 mmHg and/or diastolic arterial pressure $>$ 90 mmHg, or current use of antihypertensive drugs prescribed with the aim to reduce blood pressure.[12]

Diabetes mellitus was diagnosed according to the American Diabetes Association and defined by a fasting plasma glucose of $\geq$ 7mM or 2-hours postprandial glucose of $\geq$ 11.1mM, or current use of antidiabetic agents.[13]

Measurement of CIMT of the right and left common carotid artery was performed as per protocol described in the American Echocardiography Guidelines by a trained sonographer and verified by a consultant radiologist who was blinded to the cases.[10] Carotid ultrasound was performed by high resolution B mode (Siemens SONOLINE G40, Siemens Medical Solutions, USA) with a 7-MHz linear transducer and a transducer aperture of 38 mm. The right and left carotid arteries were scanned at the level of the bifurcation.[10] The mean from three readings was taken for 'each side' and the maximum CIMT value was recorded for analysis. CIMT values $\geq$ 75th percentile were considered increased and indicative of increased CVD risk. As there is no local reference CIMT value for our general population, the matched age and sex CIMT value from the Carotid Atherosclerosis Progression Study (CAPS) was used.[10]

Statistical analysis

SPSS Version 20.00 (Chicago, IL, USA) was used and normality testing was done for all study variables. Non-normally distributed parameters are expressed as median (interquartile range) and analyzed using nonparametric tests (Mann—Whitney *U* or Kruskal—Wallis test) for quantitative variables. Categorical variables were analyzed using chi-square tests. Correlations were tested using Spearman correlation coefficients. Univariate and multivariate analyses were performed using multiple linear and binary logistic regression. Significance was taken as $p < 0.05$. Our sample size to power the study at 80% was 36 patients in each arm.[14]

Results

Forty-six KTx patients were screened but eight had documented ischemic heart disease and hence excluded. Two patients defaulted follow-up and therefore only 36 KTx recipients and 36 controls were included in the final analysis.

There were no significant differences between KTx recipients and the controls in demographic characteristics and cardiovascular risks as shown in Table 1. Of the 36 KTx recipients, 29 (80.6%) had a live donor transplant. All patients were on triple immunosuppressive therapy with majority on calcineurin inhibitors. Ten patients were on a proliferative signal inhibitor. The causes of end-stage renal disease were glomerulonephritis ($n = 14$), diabetic nephropathy ($n = 6$), unknown cause ($n = 6$), and hypertensive nephrosclerosis ($n = 2$). The KTx recipients body mass index was 24.0 (20.7—26.3) kg/m^2. Their dialysis duration prior to transplantation was 18.5 (9.0—28.9) months and duration post renal transplantation was 76.5 (48.0—108) months. Table 2 shows the laboratory characteristics of KTx recipients.

KTx recipients had a significantly increased CIMT 0.80 (0.60—0.90) mm compared to controls 0.55 (0.50—0.70) mm

Table 1 Demographic data and clinical characteristics for both groups.

Characteristics	Kidney transplant $n = 36$ (%)	Control $n = 36$ (%)	*p*
Age (y)	41.5 (38.0,52.0)	44.5 (37.3,53.5)	0.790
Sex			
Male	25 (69.4)	25 (69.4)	>0.999
Female	11 (30.6)	11 (30.6)	
Race			
Malay	9 (25.0)	16 (44.4)	0.089
Chinese	26 (72.2)	17 (47.2)	
Indian	1 (2.8)	3 (8.4)	
Smokers	4 (11.1)	6 (16.7)	0.121
Hypertension	29 (80.6)	29 (80.6)	>0.999
Systolic BP (mmHg)	135 (127—137)	130 (117—140)	0.749
Diastolic BP (mmHg)	78 (69—85)	83 (69—90)	0.504
Mean arterial pressure	96 (88—101)	100 (86—103)	0.712
Diabetes mellitus	12 (33.3)	12 (33.3)	<0.999
CKD staging			
Stage I	4 (11.1)	4 (11.1)	>0.999
Stage II	25 (69.4)	25 (69.4)	
Stage III	6 (16.7)	6 (16.7)	
Stage IV	1 (2.8)	1 (2.8)	

Data are presented as *n* (%) or mean (interquartile range).
BP = blood pressure; CKD = chronic kidney disease.

Table 2 Laboratory characteristics of kidney transplant recipients.

Parameters	Median (IQR)
Hemoglobin (g/dL)	13.1 (11.9–14.0)
Hematocrit (%)	40.6 (37.2–43.4)
Creatinine (μM)	109.5 (89.5–121.3)
Estimated GFR (mL/min/1.73m^2)	67.5 (60.0–80.0)
Fasting blood sugar (mM)	5.2 (4.62–7.05)
HbA1C (%)	5.95 (5.40–6.93)
Low density lipoprotein (mM)	2.47 (1.94–3.01)
High density lipoprotein (mM)	1.56 (1.30–1.75)
Triglycerides (mM)	1.37 (1.03–1.84)
Total cholesterol (mM)	4.65 (4.10–5.54)
Urine protein creatinine index (g/mmol)	0.02 (0.01–0.03)
High-sensitivity C-reactive protein (mg/L)	0.65 (0.13–1.93)
Asymmetric dimethylarginine (μM)	0.94 (0.81–1.20)

GFR = glomerular filtration rate; HbA1C = glycated hemoglobin; IQR = interquartile range.

($p = 0.001$). In the control group, the patients with increased CIMT were predominantly diabetic and had a higher BP. Their median CIMT in the diabetic patients was 0.7 (0.53–0.98) mm compared to the nondiabetics 0.5 (0.4–0.6) mm, ($p = 0.01$). The control group patients with increased CIMT had a median systolic blood pressure of 142 (138–151) mmHg whereas in the normal CIMT group was 128 (115–135) mmHg, ($p = 0.006$). We also found a strong correlation between systolic blood pressure and CIMT thickness in the control group ($R^2 = 0.444$, $p < 0.001$).

In the KTx recipients, we compared clinical and laboratory parameters in patients with and without increased CIMT as shown in Table 3. On univariate analysis, we found age ($R^2 = 0.566$, $p < 0.001$) and hemoglobin ($R^2 = 0.395$, $p = 0.017$) positively correlated with CIMT measurement. There was a significant correlation between ADMA and hs-CRP ($R^2 = 0.352$, $p = 0.036$). On multiple linear stepwise regression we used age and hemoglobin on the prediction model with two steps (Table 4).

Discussion

Endothelial dysfunction and ongoing chronic inflammation due to multiple risk factors including immunosuppressive therapy play an important role in premature subclinical atherosclerosis in KTx recipients.[4,11,15] We found that the prevalence of increased CIMT was significantly higher in our KTx recipients compared to controls. These findings concur with Basiratnia et al[14] who demonstrated a higher mean CIMT in KTx recipients compared to healthy individuals. However Basiratnia et al[14] looked at healthy controls, whereas in our study, our controls were matched for CKD staging and CVD risk. We found no difference in terms of blood pressure, or diabetes or dyslipidemia between our controls and KTx recipients that could contribute to CIMT. Apart from diabetes, hypertension, and age, there are other factors that play a role in aggravation of the atherosclerosis in our KTx recipients. These could be due to their immunosuppressive therapy, microinflammation, and some effects from dialysis vintage.

Our study is the first to evaluate the prevalence of subclinical atherosclerosis by measuring CIMT among KTx recipients in Malaysia. The majority of our KTx recipients had increased CIMT and this is in keeping with several other studies.[16,17]

Kasiske et al[18] reported that 16% of KTx patients developed new atherosclerotic complications over a 10-year period and was independently associated with increasing age, male sex, cigarette smoking, the presence of diabetes mellitus, hypertension, and elevated serum cholesterol. Similarly, we observed that KTx recipients with increased CIMT had a higher low density lipoprotein (LDL), higher hemoglobin, and a shorter duration of dialysis. We also found male sex and smoking to have a trend towards significance.

Hypertension plays an important role in the development of atherosclerosis with studies demonstrating its association with increased CIMT.[19,20] We could not establish this association in our study due to the good blood pressure control in our KTx recipients and the small sample size. The high prevalence of hypertension in our study could be explained by pre-existing hypertension and the use of calcineurin inhibitors and steroids as part of maintenance immunosuppression.[21]

Dyslipidemia, a frequent and persistent complication after solid organ transplantation, contributes to cardiovascular morbidity and mortality. The pathogenesis of post-transplantation dyslipidemia is not fully understood, although several factors including age, weight, pre-transplantation lipid levels, and immunosuppressive therapy, in particular corticosteroid, cyclosporine, and proliferative signal inhibitors, are implicated.[22] Our patients with increased CIMT had a significantly higher LDL compared to those with normal CIMT and in keeping with the reported literature.[16,23] Artz et al[24] demonstrated an improvement in CVD risk profile (especially lipid profile) after switching KTx recipients from cyclosporine A to tacrolimus.

Our KTx recipients with increased CIMT had a higher hemoglobin, consistent with Toz et al.[25] We believe the association between higher hemoglobin and increased CIMT in our study could also be contributed by smoking and is consistent with several other studies.[20,26] The smokers had a trend ($p = 0.058$) towards increased CIMT over non-smokers with the four current and former smokers having a hemoglobin >15 g/dL. On further analysis, we found that the smokers had significantly higher hemoglobin than non-smokers, $p = 0.04$. Cigarette smoking after kidney transplantation has been associated with adverse cardiovascular outcomes and allograft dysfunction.[27]

In contrast to Massy,[22] we found patients with a shorter duration of dialysis had increased CIMT. On further sub-analysis, the majority of transplant patients who had dialysis for <2 years were males with dyslipidemia, hypertension and diabetes. We believe that these could have confounded our findings.

KTx recipients are believed to have a persistent low-grade inflammation that contributes to the endothelial dysfunction. Inflammation is increasingly recognized as a modifiable cardiovascular risk factor in renal disease.[4]

Table 3 Comparison among kidney transplant recipients with increased and nonthickened carotid intima-media thickness (CIMT).

Parameters	Thickened CIMT $n = 24$	Nonthickened CIMT $n = 12$	p
Age (y)	43.49 (38.25–51.5)	41.00 (33.75–63.50)	0.856
Sex			
Male	19 (52.8)	6 (16.7)	0.073
Female	5 (13.9)	6 (16.7)	
Smoking status			
Current smokers	4 (11.1)	0 (0)	0.058
Former smokers	4 (11.1)	0 (0)	
Never smokers	16 (44.4)	12 (33.3)	
Diabetes mellitus	8 (66.7)	4 (33.3)	>0.999
Hypertension	18 (50)	11 (30.6)	0.234
Blood pressure (mmHg)			
Systolic	135 (127–137)	125 (114–146)	0.416
Diastolic	78 (69–85)	77 (63–89)	0.631
Mean arterial pressure	96 (88–101)	96 (79–104)	0.608
CKD staging			
Stage I	2 (5.6)	2 (5.6)	0.173
Stage II	19 (52.8)	6 (16.7)	
Stage III	2 (5.6)	4 (11.1)	
Stage IV	1 (2.8)	0 (0)	
Types of donor			
Living	19 (52.8)	10 (27.8)	0.766
Cadaveric	5 (13.9)	2 (5.6)	
Duration of dialysis (mo)	18 (7.5–24)	30 (16.5–42)	**0.041**
Duration post transplantation (mo)	82 (47–108)	76 (57.5–118)	0.882
Creatinine (μM)	111 (91.8–121.3)	104.5 (75.5–124)	0.562
Estimated GFR (mL/min/1.73m^2)	67 (60.5–79.8)	75 (52.3–85.3)	0.886
Hemoglobin (g/dL)	13.75 (12.25–14.55)	12.35 (11.43–12.99)	**0.006**
HbA1C (%)	5.85 (5.32–6.92)	6.05 (5.45–6.93)	0.655
Fasting blood sugar (mM)	5.15 (4.65–7.58)	5.35 (4.62–6.95)	0.830
Total cholesterol (mM)	4.86 (4.37–5.91)	4.49 (3.77–5.34)	0.156
Low density lipoprotein (mM)	2.58 (2.10–3.29)	1.96 (1.53–2.65)	**0.022**
High density lipoprotein (mM)	1.57 (1.30–1.99)	1.53 (1.23–1.70)	0.476
Triglycerides (mM)	1.41 (0.92–1.79)	1.31 (1.03–2.40)	0.753
Urine PCI (g/mmol)	0.02 (0.01–0.03)	0.03 (0.01–0.03)	0.379
Hs-CRP (mg/L)	0.95 (0.53–2.75)	0.30 (0.10–1.65)	0.188
ADMA (μM)	0.96 (0.93–1.27)	0.94 (0.77–1.17)	0.280

Data are presented as n (%) or mean (interquartile range).
Values in bold indicate significant difference ($p < 0.05$).
ADMA = asymmetric dimethylarginine; CKD = chronic kidney disease; GFR = glomerular filtration rate; HbA1C = glycated hemoglobin; Hs-CRP = high-sensitivity C-reactive protein; PCI = protein creatinine index.

Studies have reported that several inflammatory markers (hs-CRP, interleukin-1 and 6, and tumor necrosis factor-α) are increased in KTx recipients.[4] However, we could not demonstrate any association between hs-CRP and CIMT due to the small sample size.

On univariate analysis, we demonstrated a positive correlation of increasing age with CIMT. This is consistent with several large studies including CAPS where increasing age has been associated with progression of atherosclerosis.[10] Aging-related mechanical and structural changes of

Table 4 Multiple linear regression.

Model	Dependent variable	Independent variables	R^2	p	R^2 change	p
1	CIMT value	Age	0.211	0.005		
2	CIMT value	Age	0.398	<0.001	0.211	0.005
		Hemoglobin			0.187	0.003

CIMT = carotid intima-media thickness.

the vascular wall cause loss of arterial elasticity, reduced arterial compliance, hardening, and stiffening of the vessel. Subsequent multiple linear regression analysis demonstrated age and hemoglobin to be the main independent predictors of CIMT.

We did not have baseline CIMT measurements pre-transplantation to establish significant progression of sub-endothelial dysfunction. Our small sample size was the main limitation that may cause bias in our results. Another limitation in our study was the reference for normal values of CIMT. As there are limited data among the East Asian population, we had to resort to the use of CAPS for reference, which is derived from Caucasians who have dissimilar sociodemographic and genetic background from Asians.[10] We feel that we may have underestimated the cardiovascular risk in our patients.

In conclusion, our study demonstrated a higher prevalence of increased CIMT among KTx recipients compared with matched (age, sex, CKD staging, and CVD risk) controls. Age and hemoglobin were important independent risk predictors for increased CIMT. More than half of our KTx recipients are at increased risk of cardiovascular disease and a multitargeted approach is important to reverse the progression of atherosclerosis. Larger prospective studies are indicated to establish better association between all the cardiovascular risks with CIMT in KTx recipients.

Conflicts of interest

All authors declare no conflicts of interest.

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